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Optimal Use of Dobutamine Stress for the Detection and Evaluation of Coronary Artery Disease: Combination With Echocardiography or Scintigraphy, or Both?

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Objectives. **This study was conducted to examine the efficacy of dobutamine stress two-dimensional echocardiography and perfusion scintigraphy for the detection of coronary artery disease in routine practice, to establish the causes of erroneous results and to derive appropriate criteria for the selection of either or both tests.**

Background. **Dobutamine stress combined with echocardiography or perfusion scintigraphy may be used to detect coronary artery disease. Although both imaging approaches have demonstrated similar levels of accuracy, it is not known whether there may be particular indications for the use of one or the other technique or a rationale for their combination.**

Methods. **Two hundred seventeen patients without previous infarction were studied prospectively with dobutamine stress echocardiography and technetium-99m methoxy isobutyl nitrile (sestamibi) single-photon emission computed tomography at the time of diagnostic coronary angiography. The presence of coronary stenoses of ≥50% diameter was compared with the presence of rest or stress-induced abnormalities of perfusion and regional function. The extent of these abnormalities was correlated with an equivalent score of extent of angiographic disease.**

Results. **Significant coronary artery disease was found in 142 patients; 102 (72%) were identified by dobutamine echocardiography and 108 (76%, p = NS) by perfusion imaging. In 75 patients without significant disease, the specificity of dobutamine echocardiography was 83% compared with 67% for scintigraphy (p = 0.05). Echocardiographic sensitivity was lower in patients unable to complete the test because of side effects (n = 64) than in the remainder (59% vs. 77%, p = 0.02); this influence was less apparent with scintigraphy (71% vs. 78%, p = NS). Selective use of scintigraphy in the 31 patients with a negative submaximal stress echocardiogram led to a sensitivity of 80% for this combination. Patients with left ventricular hypertrophy accounted for most of the difference in specificity between echocardiography and scintigraphy (94% vs. 59%, p = 0.02). Their respective accuracies were 76% and 73%.**

Conclusions. **Dobutamine stress echocardiography and perfusion scintigraphy have equivalent accuracy. In patients with left ventricular hypertrophy, echocardiography appears to be the test of choice. Selective use of sestamibi scintigraphy in patients with a negative submaximal echocardiogram enhances the accuracy of stress echocardiography alone.**

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Existing comparisons of exercise echocardiography and perfusion scintigraphy have shown them to have comparable levels of accuracy in the diagnosis of coronary artery disease (1–5). In patients who cannot exercise, the same appears to be true of dobutamine stress echocardiography and perfusion scintigraphy (6), although the latter appears to be significantly more accurate if vasodilator stressors are used (6–8). To date, however, no study has identified particular subgroups that are best studied by either stress echocardiography or perfusion scintigraphy, or both, in a routine clinical context. Antianginal therapy and submaximal tests may be more difficult to avoid under these conditions than in a focused study involving smaller numbers of patients. Moreover, although noninvasive studies enable an assessment of the extent of ischemia as well as its diagnosis, the ability of these techniques to predict the extent of coronary disease has not been compared.

The purpose of this study was to compare a large series of patients studied with both dobutamine stress echocardiography and dobutamine stress perfusion scintigraphy in a routine clinical setting and establish the relative accuracy of the tests and their ability to predict the extent of coronary artery disease. False negative and false positive results were examined to identify if they were associated with particular patient subgroups and to determine whether a selective

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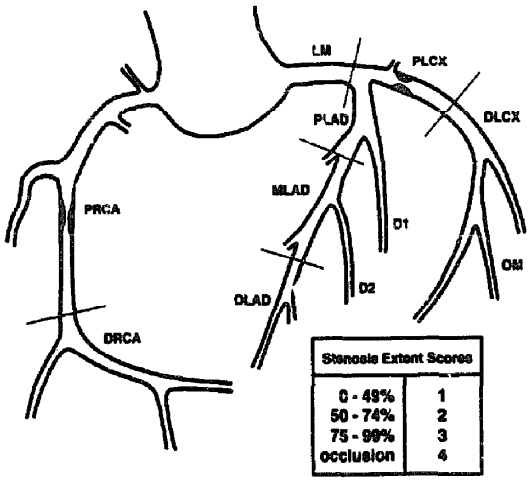

LOCATION SCORES		
SITE OF STENOSIS		MULTIPLE (of stenosis score)
LM	LEFT MAIN	x 5
PLAD	PROXIMAL LEFT ANTERIOR DESCENDING	x 2.5
MLAD	MID LEFT ANTERIOR DESCENDING	x 1.5
DLAD	DISTAL LEFT ANTERIOR DESCENDING	x 1
D1	FIRST DIAGONAL	x 1
D2	SECOND DIAGONAL	x 0.5
PLCX	PROXIMAL LEFT CIRCUMFLEX	x 2.5 or 2
DLCX	DISTAL LEFT CIRCUMFLEX	x 1 or 0.5
OM	OBTUSE MARGINALS	x 1 or 0.5
PRCA	PROXIMAL RIGHT CORONARY	x 1
DRCA	DISTAL RIGHT CORONARY	x 1

Figure 1. Angiographic score of extent of coronary artery disease. In each of 11 coronary segments, a stenosis score is multiplied by a correction factor (reflecting the relative size of the vessel) and the resulting scores are summed. Each score is expressed as a percent of the maximal score in that patient (to compensate for differences in maximal scores due to variations in coronary anatomy). For example, in a patient with 75% stenoses in the proximal right coronary and proximal circumflex arteries, the individual scores would be 3 (1 × 3) and 7.5 (2.5 × 3), respectively, totaling 10.5 (15%) of a possible total score of 72, assuming that all branches are large enough to justify the maximal score.

combination of both techniques could enhance the accuracy of one approach alone.

Methods

Patient selection. Patients presenting for diagnostic coronary angiography were prospectively recruited into the study over a 12-month period if they had no historical or electrocardiographic (ECG) evidence of previous myocardial infarction. After the exclusion of those with unstable angina, malignant arrhythmias, cardiomyopathy, severe valvular disease or severe hypertension (systolic pressure >200 mm Hg, diastolic pressure >120 mm Hg), 217 patients consented to undergo dobutamine stress testing with both echocardiography and perfusion scintigraphy in a protocol approved by the Institutional Review Board. This group comprised 156 men and 61 women, aged 58 ± 10 years. Typical angina was present in 142 (65%); the remaining 75 patients had symptoms sufficiently suggestive of coronary artery disease to warrant angiography. The pretest probability of disease, calculated for each patient on the basis of age, gender and the clinical history (9), was 54 ± 28%. An intermediate level (20% to 80%) of pretest probability was present in 131 patients and 46 had a high (>80%) and 40 had a low (<20%) pretest probability of coronary artery disease.

Coronary arteriography. Coronary arteriography was performed using the Judkins technique in all patients. All films were read by experienced observers, one of whom quantitated coronary stenoses by manual tracing and measurement in as close as possible to orthogonal projections, using a technique previously validated with computer-assisted quantitative angiography (10). Significant disease (identified by >50% diameter stenosis in a major epicardial coronary artery) was present in 142 patients, of whom 68 had single-vessel disease (defined by >50% stenoses confined to one coronary artery or its major branches, or both). The remaining patients without significant disease had either normal coronary arteries (n = 66) or <50% stenoses (n = 9).

A modification of the Gensini score (11) was used to reflect the extent of the stenoses. Total scores were obtained from the sum of 11 regional scores derived from the product of stenosis location and stenosis dimension components. Points allocated for stenoses (0 to 4) in different segments were weighted to reflect proximal or distal location in the coronary tree; to correct for variations in coronary anatomy, this weighting could be modified (Fig. 1). To ensure comparability among patients, the score was expressed as a percent of the maximal possible score for the coronary anatomy in each patient.

Dobutamine stress. Patients underwent stress testing during the hospital admission for cardiac catheterization. Although they were advised to avoid antianginal therapy on the day of the test, 42 took beta-adrenoreceptor antagonists and 55 took nitrates or calcium antagonists, or both; the protocol was performed as planned in these situations to correspond to the equivalent clinical circumstance. Before the test was started, a clinical history was taken by one investigator to calculate the pretest probability of disease (9). After routine preparation, a rest ECG and echocardiogram were performed, intravenous access was secured and dobutamine was infused in 3-min dose increments from 5 to 40 μg/kg per min under continuous ECG and echocardiographic monitoring (12,13). The test was concluded after achievement of the peak dose or earlier if the patient developed severe ischemia (either severe angina or severe impairment of left ventricular function) or intolerable side effects. These "submaximal" doses were caused by hypertension (systolic pressure

>220 mm Hg, diastolic pressure >120 mm Hg), hypotension (>20 mm Hg decrease from peak systolic pressure), dyspnea or arrhythmias. Clinical signs and the ECG and echocardiographic images were recorded at the beginning of the study and every 3 min thereafter until after the conclusion of the stress. Technetium-99m methoxyisobutyl nitrile (sestamibi) (20 mCi) was injected intravenously 1 to 2 min before the conclusion of the infusion, except when severe side effects necessitated termination of the test. In this circumstance, this interval was shortened if it was considered unsafe to continue the dobutamine even at a lower dose.

Stress electrocardiography. The ECG was monitored and digitized throughout the stress protocol using the Frank leads. The presence of ischemia was identified by ≥0.1 mV of horizontal or downsloping ST segment depression or ≥0.1 mV ST segment elevation at an interval of 0.06 s after the J point. Chest pain, the presence and nature of limiting symptoms and side effects of the stress agent were recorded.

Two-dimensional echocardiography. Echocardiographic images in parasternal long- and short-axis and apical four- and two-chamber views were digitized online (PreVue, Nova Microsonics). The rest, 10-, 30- and 40-μg/kg per min stages were recorded digitally in quadscreen, cineloop format on 5.25-in. (13.3 cm) floppy disks, and all stages were recorded on videotape. Data of satisfactory quality were obtained in 209 patients (96%), but echocardiograms were interpreted for all subjects.

Images were interpreted qualitatively in accordance with previous guidelines (14) by experienced observers who had no knowledge of the angiographic, scintigraphic and clinical data. A normal response was defined by a homogeneous enhancement in contractility with stress. Ischemia was identified by a stress-induced wall motion abnormality, including failure to improve wall motion relative to hyperkinetic responses to maximal stress. Infarction was defined by akinesia and dyskinesia at rest. Because of the potential for hypokinesia at rest in normal myocardium (15), such areas were interpreted as normal if they showed improved function with dobutamine and abnormal if they failed to improve.

Regional function was interpreted in 16 myocardial segments (at basal, midventricular and apical levels of the septum; lateral, anterior and inferior walls; and basal and midventricular levels of the anteroseptal and posterior walls). These were combined to reflect the territories of the coronary arteries as previously described (15); the anterior, apical, septal and anteroseptal walls were ascribed to the left anterior descending; the posterior and lateral to the left circumflex, and the inferior and basal septal segments to the right coronary artery. An extent score was calculated from the number of segments demonstrating abnormal regional function, expressed as a percent of the visible segments (usually all 16). Finally, echocardiographic images were interpreted for the presence of left ventricular hypertrophy (defined by diastolic wall thickness >12 mm in the parasternal long-axis view).

Perfusion imaging. Perfusion scintigraphy was performed 1 to 2 h after the injection of technetium-99m sestamibi. Rest and stress scans were normally done on successive days; if a "same day" protocol (16) was necessary because of scheduling considerations, rest and stress injections were separated by 6 h, with the rest scan (using only 5 mCi of technetium-99m sestamibi) performed before stress scintigraphy. Scintigraphic data were acquired over 180° using a large field, single-crystal camera and high resolution collimator (General Electric 400 AC/T). Transaxial images were obtained by back-projection using a Shepp-Logan filter, then reoriented into short-axis and vertical and horizontal long-axis views.

Perfusion scintigraphy was interpreted by experienced observers who had no knowledge of the clinical, echocardiographic and angiographic characteristics of the patient. A qualitative comparison between stress and rest images was made using the same segmentation as that employed for echocardiography, and the same assumptions were made about the coronary artery distributions. An analogous defect extent score was derived by expressing the number of abnormal segments as a percent of the total. Regions were then interpreted as showing normal perfusion, a stress-induced perfusion defect or a fixed perfusion defect.

Statistical analysis. The sensitivity, specificity and positive and negative predictive accuracy of dobutamine stress echocardiography and technetium-99m sestamibi scintigraphy were obtained in the usual fashion. Odds ratios were derived as follows: for a positive test (1 − specificity)/sensitivity and for a negative test, specificity/(1 − sensitivity). These values and the pretest probability of disease were used to calculate the posttest probability of disease using Bayes theorem. The pretest and test variables correlating with false positive and false negative scans were also identified. The results of a combined imaging approach were investigated in these subgroups and in the group as a whole. The results for each different test were compared using the McNemar test for paired data. Continuous variables were expressed as mean value ± SD and compared using a paired *t* test; unpaired data were compared with a chi-square (with or without Yates correction) or Fisher exact test, depending on the sample size. Results of the wall motion and perfusion defect extent scores were compared with the angiographic scores in a linear regression analysis.

Results

Dobutamine stress response. In the overall group, dobutamine increased the heart rate by 42 ± 22 beats/min to a peak heart rate of 109 ± 25 beats/min. Blood pressure increased to 178 ± 23 mm Hg and an average peak rate-pressure product of 19,400 ± 5,300. Electrocardiographic evidence of ischemia (≥0.1-mV ST segment depression or elevation) was induced in 37 patients. Prediction of coronary artery disease based on the use of ECG changes alone thereby gave a sensitivity of 28% in 131 patients with

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Table 1. Distribution of Patients With and Without Significant Coronary Artery Disease (CAD) With Positive (Pos) or Negative (Neg) Findings by Electrocardiographic and Chest Pain Criteria (ECG), Stress Echocardiography (Echo) and Perfusion Scintigraphy (Mibi-SPECT) After Dobutamine Stress

	ECG		Echo		Mibi-SPECT	
	Pos	Neg	Pos	Neg	Pos	Neg
Patients with CAD (n = 142)	74	68	102	40	108	34
Patients without CAD (n = 75)	24	51	13	62	25	50

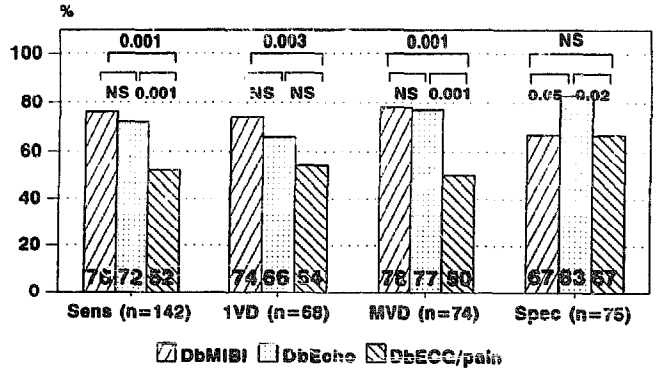

Figure 2. Results of dobutamine (Db) stress technetium-99m sestamibi perfusion scintigraphy (MIBI), echocardiography (Echo) and electrocardiographic (ECG) changes or angina (pain) for the diagnosis of coronary artery disease. 1VD = sensitivity in those with single-vessel disease; MVD = sensitivity in patients with multivessel disease; Sens = overall sensitivity; Spec = specificity.

coronary artery disease and an interpretable ECG and a specificity of 94%. Use of either ST segment changes or chest pain, or both, gave a sensitivity of 52%, a specificity of 67% and an overall accuracy of 57%.

Significant side effects were experienced by 84 patients (39%), and the test was terminated before peak dose in 64 patients (29%). The most frequent side effect was hypotension (n = 36), most commonly asymptomatic (in 32 patients). Arrhythmias precipitated conclusion of the test in eight patients (one with nonsustained ventricular tachycardia, three with complex ventricular extrasystoles and five with supraventricular tachyarrhythmias). Other side effects included hypertension (n = 9), dyspnea (n = 7), vagal reactions (n = 2) and anxiety (n = 2). The high incidence of side effects was attributable in part to the inclusion of ischemia as an end point only in the presence of severe angina or extensive left ventricular dysfunction. Milder ischemia was present in 33 of the 64 patients before the onset of side effects, so 31 patients (14%) had a nondiagnostic echocardiogram due to submaximal stress.

Detection of "significant" coronary artery disease. The numbers of patients with and without coronary artery disease with a positive or negative dobutamine stress ECG result (including angina) echocardiography and scintigraphy are summarized in Table 1. One hundred forty-two patients had significant (≥50% diameter) stenoses; 102 were identified by dobutamine echocardiography (sensitivity 72%), compared with 108 by dobutamine technetium-99m sestamibi perfusion scintigraphy (sensitivity 76%, p = NS). Both imaging techniques (Fig. 2) were more sensitive than dobutamine ECG (sensitivity 52%, $p < 0.001$). In 75 patients with mild or no coronary artery disease, the specificity of echocardiography and scintigraphy was, respectively, 83% and 67% (p = 0.05); the former (but not the latter) was more specific than dobutamine electrocardiography (specificity 68%, p = 0.02). The overall accuracy of dobutamine echocardiography, scintigraphy and electrocardiography were 76%, 73% and 57%, respectively (p = NS). The predictive value of the 115 positive dobutamine echocardiographic results was 89%, compared with 81% for the 133 positive dobutamine scintigraphic results (p = NS); the respective predictive values of a negative echocardiographic and scintigraphic result were 59% and 60%. Moreover, the odds ratios for a positive echocardiogram (0.24) and scintigram (0.43) were similar, as were the odds ratios for a negative echocardiogram (2.96) and a negative scintigram (2.30).

Seventy-four patients had coronary stenoses in multiple vessels. In this group, dobutamine echocardiography had a sensitivity of 77% and scintigraphy had a sensitivity of 78% (p = NS); both tests were more sensitive than dobutamine ECG (sensitivity 50%, $p < 0.001$). Neither the sensitivity of stress echocardiography nor that of perfusion scintigraphy was significantly greater in multivessel than in single-vessel disease. Among 68 patients with single-vessel disease, technetium-99m scintigraphy had a slightly greater sensitivity than that of dobutamine echocardiography (74% vs. 66%, p = NS) and only scintigraphy was more sensitive than dobutamine electrocardiography in this group (74% vs. 54%, p = 0.003). Neither test was found to be superior on a regional basis; in 34 patients with only left anterior descending territory disease, the sensitivity of echocardiography was 62%, compared with 76% by scintigraphy (p = NS) and in 34 with only left circumflex or right coronary artery disease, both tests had a sensitivity of 71%.

Using the presence of ≥70% stenosis as the determinant of significant disease, echocardiography had a sensitivity of 73% in the 135 patients with significant coronary artery disease, a specificity of 79% and an accuracy of 75%. The respective values for scintigraphy were 77% (p = NS), 65% (p = 0.05) and 72% (p = NS).

Classification into high, low and intermediate risk subgroups. The posttest probability of coronary artery disease was used to define three subgroups at high (>80%), intermediate (20–80%) and low probability (<20%) of disease. By application of Bayes theorem, echocardiography defined 139 patients (64%) as being in the high or low probability groups, compared with 110 (51%) studied by scintigraphy (p = 0.005), thus leaving more patients in the intermediate probability group after scintigraphy. The accuracy of predicting coronary disease in the high probability group and

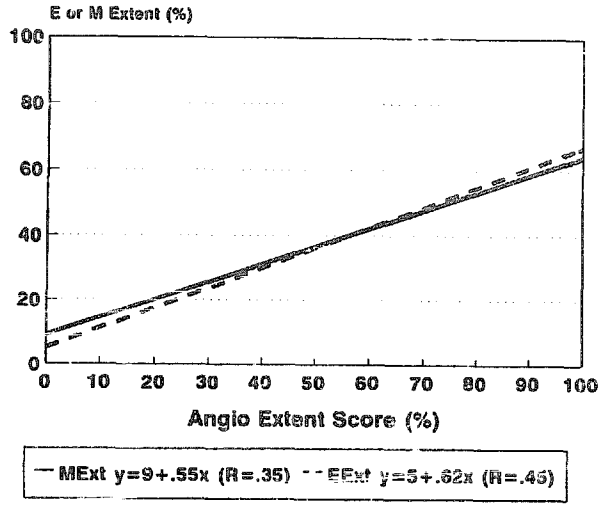

Figure 3. Relation between angiographic (Angio) score of extent of coronary artery disease with the equivalent echocardiographic (EExt, **dashed line**) and scintigraphic scores (MExt, **solid line**) (each score is expressed as a percent of the maximal score).

the absence of disease in the low probability group were similar for echocardiography (120 [86%] of 139 patients) and scintigraphy (99 [90%] of 110 patients).

Prediction of the extent of coronary artery disease. Of the 74 patients with multivessel coronary disease, functional abnormalities were seen in >1 coronary territory in 18% of dobutamine stress echocardiograms, and 34% of scintigrams (p = NS). However, this benefit of perfusion imaging was tempered by being somewhat less specific for multivessel disease, which was predicted by scintigraphy in 19% of patients actually having single-vessel disease, compared with 9% of those with single-vessel disease wrongly predicted to have multivessel disease by echocardiography.

The correlation of angiographic disease extent (modified Gensini score) with the equivalent echocardiographic and scintigraphic extent scores is depicted in Figure 3. The greater Y intercept of the scintigraphic approach mirrors the lower specificity of this technique (whereby patients with a low or zero angiographic score may have abnormal perfusion). Defect extent scores by echocardiography and scintigraphy had essentially the same regression coefficient, with the former having a slightly higher r value. These data suggest that functional and perfusion indexes of extent of coronary artery disease are comparable and consistent with similar overall accuracy in predicting (but underestimating) multivessel disease.

Correlates of false negative results. The relation of false negative echocardiographic and scintigraphic results to clinical, angiographic and stress variables is summarized in Table 2.

False negative dobutamine echocardiographic results correlated with the performance of a submaximal stress test (premature termination of the test because of side effects). False negative results also tended to correlate with a less vigorous stress response (evidenced by lower peak heart rate and heart rate increment) and less extensive coronary artery disease (evidenced by a greater prevalence of single-vessel disease and a lower modified Gensini score). These factors were also apparent among patients with false negative dobutamine perfusion scintigrams, but none of the factors achieved statistical significance. There was also a trend toward a higher prevalence of patients taking beta-blockers on the day of the test among patients with false negative

Table 2. Correlates of False Negative Results for Dobutamine Stress Echocardiography and Perfusion Scintigraphy

	Echocardiography (E)			False Negative	Scintigraphy (S)		
	True Positive	p Value	False Negative	(E vs S)	False Negative	p Value	True Positive
Patients (no.)	102		40		34		108
Age (yr)	60 ± 9	NS	60 ± 8	NS	58 ± 9	NS	60 ± 8
Female gender	16 (16)	0.03	13 (33)	NS	13 (38)	0.01	16 (15)
Beta-blockade	18 (18)	NS	11 (28)	NS	10 (29)	NS	19 (18)
Left bundle block	3 (3)	NS	0 (0)	NS	0 (0)	NS	3 (3)
LV hypertrophy	27 (26)	NS	10 (25)	NS	8 (24)	NS	29 (27)
Angiographic							
Multivessel CAD	57 (56)	NS	17 (43)	NS	16 (47)	NS	58 (54)
CAD extent score	15 ± 9	NS	11 ± 6	NS	11 ± 6	NS	14 ± 9
Ejection fraction (%)	65 ± 8	NS	67 ± 10	NS	70 ± 8	NS	64 ± 9
Dobutamine stress							
Peak HR (beats/min)	108 ± 25	NS	103 ± 24	NS	102 ± 28	NS	107 ± 23
HR increment (beats/min)	43 ± 23	NS	35 ± 24	NS	36 ± 26	NS	42 ± 24
Peak BP (mm Hg)	178 ± 27	NS	177 ± 21	NS	170 ± 25	NS	179 ± 21
Submaximal test	24 (24)	0.02	17 (43)	NS	12 (35)	NS	29 (27)
ST depression (mm)	23 (23)	NS	10 (25)	NS	3 (9)	0.04	30 (28)

Data are expressed as mean value ± SD or number (%) of patients. BP = blood pressure; CAD = coronary artery disease; HR = heart rate; LV = left ventricular.

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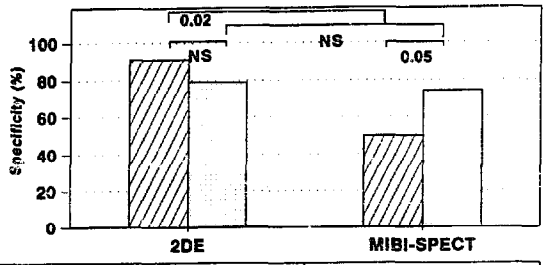


LVH/LBBB (n=22)	91	50
Remainder (n=53)	79	74

Figure 4. Specificity of dobutamine stress echocardiography (2DE) and perfusion scintigraphy with technetium-99m sestamibi (MIBI-SPECT) in patients with left ventricular hypertrophy (LVH) or left bundle branch block (LBBB) compared with that in the remaining patients with no coronary artery disease and without these abnormalities.

results for either test. Exclusion of 31 dobutamine echocardiograms and 29 dobutamine scintigrams as nondiagnostic (a negative test result in the setting of submaximal stress) led to their respective sensitivities increasing to 82% and 83%, with specificities of 79% and 57%.

Table 2 also shows a significantly increased prevalence of false negative results by both techniques in women. This probably reflects the presence of a milder degree of coronary artery disease in women; 10 of the 13 women with false negative echocardiographic findings and 9 of 13 with false negative scintigraphic results had single-vessel disease. Thus, examination of the sensitivity of echocardiography (76%) and scintigraphy (81%) in men slightly exceeded the results for the overall group. The same was true with respect to the specificity of echocardiography (88%) and scintigraphy (74%) in men.

The only other significant correlate was a lower prevalence of ST segment depression among those with false negative scintigraphic results—a manifestation of less severe ischemia in this group. The fact that this finding was not a significant correlate of false negative echocardiograms may imply that the latter events may be related to other factors (such as image quality), as much as to the absence of ischemia.

Correlates of false positive results. Dobutamine stress echocardiography was significantly more specific than dobutamine perfusion scintigraphy in all 75 patients with <50% stenoses (Fig. 2). The false positive scintigrams were not attributable to soft tissue attenuation; of the 25 studies with false positive findings, only 1 showed a rest perfusion defect and 10 showed a combination of rest and stress defects. They were also not clearly attributable to mild ("subsignificant") coronary lesions; in 66 patients with no stenoses, echocardiography had a specificity of 82%, compared with 68% by perfusion imaging. Among the nine patients with "nonsignificant" stenoses, the respective specificities were 89% and 56%.

The difference in echocardiographic and scintigraphic specificity was particularly pronounced in the 17 patients with left ventricular hypertrophy but without coronary artery disease, in whom the specificity of echocardiography (94%) was significantly greater than that of scintigraphy (59%, p = 0.02). A similar difference was found between the specificity of echocardiography (67%) and that of scintigraphy (17%), in six patients with left bundle branch block although the number of patients in this subgroup prevented this difference from reaching statistical significance. Classifying the patients with <50% stenosis into subgroups with and without these abnormalities (Fig. 4), it is apparent that the lower specificity of dobutamine scintigraphy is chiefly attributable to the false positive results associated with left ventricular hypertrophy and left bundle branch block. Indeed, scintigraphy in this group is associated with lower specificity than that of scintigraphy in patients without these abnormalities (p = 0.05), as well as lower specificity than that of echocardiography (p = 0.02). Moreover, Table 2 shows that the superior specificity of echocardiography in these patients is not achieved at the cost of compromising sensitivity.

Combination of echocardiography and scintigraphy. Perfusion scintigraphy may be incorporated with all or some of the dobutamine stress echocardiograms; the values of sensitivity and specificity using four combined approaches are compared in Figure 5. The first combined approach is the use of both tests in all patients. This maximizes the sensitivity (89%), but combines the false positive results of each method (specificity 52%). A more focused use of scintigraphy, in the 102 patients with negative echocardiographic findings, produces the same results with fewer scintigrams, even though this option requires on-line interpretation. The third alternative is to use echocardiography as the preliminary test, combining with technetium-99m sestamibi perfusion scintigraphy in those undergoing submaximal stress, except those with left ventricular hypertrophy and left bundle branch block. This limits the number of scintigrams (n = 64) and gives a high sensitivity without compromising specificity to the same extent. Finally, the use of scintigraphy only in those with negative submaximal dobutamine echocardiographic findings may further limit the number of required studies (n = 30) while at the same time increasing the sensitivity of dobutamine echocardiography alone. However, none of these combinations significantly enhances the overall accuracy of dobutamine echocardiography alone.

Among 40 patients with a low probability of disease, stenoses were present in 13. In this group, echocardiography and perfusion imaging had a respective sensitivity of 54% and 85% (p = NS), specificity of 85% and 78% (p = NS) and accuracy of 78% and 80% (p = NS). In the 46 patients at high risk of coronary artery disease, echocardiography and scintigraphy had a respective sensitivity of 84% and 80% (p = NS), specificity of 100% and 0% and accuracy of 87% and 76% (p = NS).

Discussion

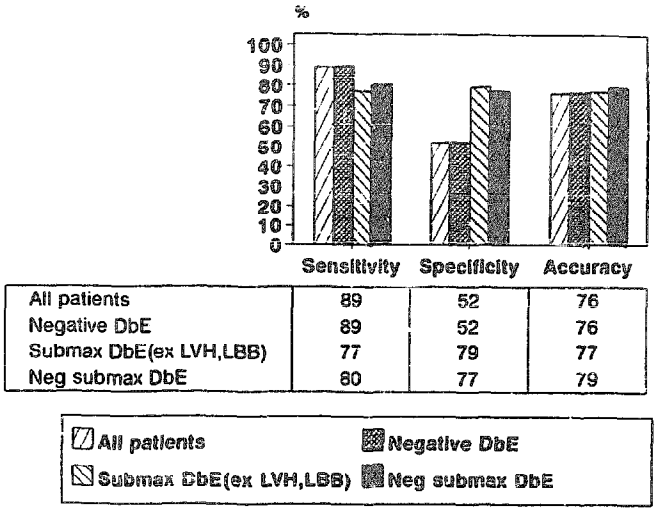
This study compared the results of echocardiography and perfusion scintigraphy at the same dobutamine stress level in patients without previous Q wave myocardial infarction. This comparison was made in a large unselected series, reflecting appropriate patient selection for noninvasive testing for coronary artery disease (pretest probability 54 ± 28%) under the usual clinical circumstances at a tertiary referral center. The results suggest that dobutamine echocardiography has comparable sensitivity to dobutamine stress perfusion scintigraphy and that the extent of perfusion and wall motion defects shows a similar correlation with the anatomic extent of coronary artery disease. In the situation of milder degrees of ischemia due to single-vessel coronary artery disease or that induced by submaximal stress, perfusion scintigraphy is more sensitive than echocardiography. Conversely, echocardiography appears to be more specific than perfusion scintigraphy in patients with left ventricular hypertrophy or left bundle branch block. Interpretation of dobutamine stress tests on the basis of stress-induced chest pain or ECG changes, or both, is associated with an unacceptably low level of sensitivity and specificity.

Sensitivity of echocardiography and perfusion imaging with dobutamine stress testing. Dobutamine is probably the agent of choice for pharmacologic stress echocardiography, more effectively inducing ischemia than dopamine, dipyridamole or adenosine (6,17,18). Increased cardiac work and coronary vasodilation due to dobutamine also augment coronary flow, permitting the combination of dobutamine stress testing with perfusion scintigraphy (19,20).

The findings of this study are consistent with the underlying mechanisms of the action of the tests. The high concordance of dobutamine echocardiographic and perfusion scintigraphic results reflects the fact that increased cardiac work is a common pathway to both ischemia and perfusion heterogeneity, which are induced commensurately. Despite this common pathway, alterations of regional perfusion precede the development of ischemia—this may account for the higher sensitivity of perfusion imaging in the situation of submaximal stress and milder coronary disease. These findings are concordant with the microsphere measurements of flow by Fung et al. (18) in an experimental model.

Although the relation between echocardiography and scintigraphy reported in this study is concordant with underlying principles of the tests, the accuracy levels are different from those recently reported. The lower sensitivity of dobutamine echocardiography may relate to patient selection. Sawada et al. (12) defined the safety and efficacy of the technique, finding a sensitivity of 89% for the detection of >50% stenoses in 35 patients with a normal rest echocardiogram and a specificity of 85%. However, in contrast to our use of angiography in all patients undergoing dobutamine echocardiography, the 103 patients in the latter study were selected for angiography from a total of 202 undergoing the test in a 15-month period. This process may have introduced posttest referral bias (21); patients with positive test findings have these confirmed at angiography, whereas false negative results may never be identified as such. Hence, the reported sensitivity may exceed that available in routine practice. In the study of Cohen et al. (13), a high sensitivity was favored by other aspects of patient selection—exclusion of patients with a submaximal test (who tended to have false negative results in our study) and inclusion of patients with prior infarction (which tends to inflate sensitivity values) (22). Finally, the circumstances of the test may be important. Our previous experience (6) described the results of dobutamine stress in a controlled study group in which only 3% of patients took beta-adrenoceptor antagonists on the day of the test and 12% had nondiagnostic tests. Under these circumstances, we reported the sensitivity of dobutamine echocardiography to be 85% and that of dobutamine technetium-99m sestamibi perfusion scintigraphy to be 80%.

Similarly, in previous studies of dobutamine stress perfusion scintigraphy (19,20), the reported levels of both sensitivity (94% to 97%) and specificity (80% to 87%) exceeded the results obtained in our study. With respect to sensitivity, this finding again reflects selection considerations, as both of the latter studies included patients with prior myocardial infarction, which tends to inflate values for sensitivity of both perfusion imaging and echocardiography (23). A procedural difference may also be important; both previous studies used thallium-201, so that scintigraphy was performed soon after stress and some ischemia-induced wall motion abnormalities were probably still present, augmenting relative perfusion defects by partial volume effects. This poten-



	Sensitivity	Specificity	Accuracy
All patients	89	52	76
Negative DbE	89	52	76
Submax DbE(ex LVH,LBB)	77	79	77
Neg submax DbE	80	77	79

Figure 5. Sensitivity, specificity and accuracy of combinations of perfusion scintigraphy with technetium-99m sestamibi; in all patients (n = 217), in those with negative findings on dobutamine echocardiography (DbE, n = 103), in those with a submaximal (Submax) dobutamine stress test excluding (ex) patients with left ventricular hypertrophy (LVH) or left bundle branch block (LBB) and in patients with negative (Neg) findings on submaximal dobutamine echocardiography (n = 31).

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tial influence of postdobutamine hypokinesia is avoided by the performance of technetium-99m sestamibi imaging 1 to 2 h after the stress. Finally, the lower scintigraphic specificity evident in our series probably reflects the study of a larger and unselected group, including patients with left ventricular hypertrophy and left bundle branch block.

Correlates of false negative and false positive results. False negative dobutamine echocardiographic results correlate with milder degrees of coronary artery disease. This relation, which is also found with exercise echocardiography (22), implies that patients with coronary artery disease but false negative results on stress echocardiography may follow a benign clinical course—a contention supported by follow-up studies (24). This association probably also explains the higher incidence of false negative results in women, who had less extensive coronary disease in our series.

The association of erroneous results with pretest or test variables may be of more practical clinical value. Such correlations may provide the means to select patients for echocardiographic or scintigraphic imaging, modify the interpretation of results or even permit the selective use of combined imaging approaches. In this respect, the most pertinent correlate of false negative dobutamine echocardiographic results was the performance of a "submaximal" test (in which the stress was limited by side effects). Interestingly, a recent study (25) of dobutamine echocardiography using a lower maximal dose (albeit in longer stages) showed lower levels of sensitivity than those discussed here. This effect of submaximal doses may be analogous to false negative findings with submaximal exercise stress (14), although the latter is more readily defined on the basis of blunted physiologic responses, which were less predictive in this series. False negative findings also weakly correlated with beta-adrenoceptor blocker therapy on the day of the test. Although false negative scintigraphic results showed some association with these variables, this was less marked than with echocardiography and failed to reach statistical significance. The implications of these findings are that negative submaximal dobutamine echocardiographic results should be classified as nondiagnostic and that beta-adrenoceptor antagonists should be withheld if possible on the day of dobutamine stress testing. In these circumstances, there may also be a role for the combination of scintigraphy with echocardiography. The combination of atropine with dobutamine stress was recently reported (26) to circumvent the problems posed by beta-blockade and is another alternative.

In contrast to false negative results, no clear correlates of false positive dobutamine echocardiographic findings were discernible. The major sources of false positive scintigraphic data were patients with left ventricular hypertrophy and left bundle branch block, which are recognized to be problematic areas with perfusion scintigraphy (27,28). Left ventricular hypertrophy has been previously associated with higher values of specificity at perfusion scintigraphy (29). Our findings support those of individual studies of echocardiography and scintigraphy and limit the applicability of dobutamine perfusion scintigraphy in unselected patients.

Efficacy of combinations of echocardiography and scintigraphy. The different weaknesses of echocardiography and scintigraphy suggest that some benefit may be obtained by combining these techniques. The use of a combined approach in all patients doubles the use of resources with little benefit; it increases the sensitivity to 89% but combines the false positive results of both techniques, so that the overall accuracy is not enhanced. Because the use of technetium-99m sestamibi does not require immediate imaging, it is possible to combine this approach with a dobutamine echocardiographic test only if the results of the latter is negative; this approach limits cost and may be useful in circumstances when a sensitive test is required. However, because the echocardiograms in this protocol were interpreted "off-line," this approach requires further study.

An alternative design for combined imaging is to focus on the problems posed for echocardiography by submaximal tests but to avoid the use of perfusion scintigraphy in those with left ventricular hypertrophy or left bundle branch block. This minimally enhances the sensitivity of echocardiography because scintigraphy is also compromised by submaximal tests (though to a lesser degree). Again, the number of patients requiring combined imaging may be reduced by using this approach only in patients with no echocardiographic evidence of ischemia. However, in summary, the efficacy of combined imaging approaches probably does not justify the expense involved, although the use of technetium-99m sestamibi in patients with a negative result on a submaximal test may be worthwhile.

Evaluation of coronary artery disease with echocardiography or scintigraphy. In addition to their use in noninvasive diagnosis of coronary artery disease, these techniques are also used to evaluate the degree of such disease. Although scintigraphy is more sensitive for the correct prediction of multivessel disease, its specificity for this problem is less than that of echocardiography. Their comparable accuracy in this regard is underscored by similar levels of correlation between echocardiographic and scintigraphic scores and the angiographic score of extent of disease. Thus, neither of the two imaging approaches is clearly superior for evaluating the extent of coronary disease.

Conclusions. The results of this study suggest that dobutamine stress echocardiography and perfusion scintigraphy share comparable levels of accuracy for the identifying coronary artery disease in patients without myocardial infarction. Echocardiography is at a disadvantage for the identification of milder degrees of coronary disease, and with submaximal stresses, but it is more specific. The tests appear to be equally effective for the evaluation (rather than the identification) of coronary disease. Finally, in most patients, the combination of echocardiography with scintigraphy does not produce a sufficient increment in accuracy to justify the additional expense of this approach.

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